PROPOSED SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name	Active Compression Decompression (ACD) Cardiopulmonary Resuscitation (CPR) Device and Impedance Threshold Device (ITD)
Device Trade Name	ResQCPR® System: ResQPUMP® (ACD-CPR device) and ResQPOD® ITD 16
Applicant's Name & Address	Advanced Circulatory Systems, Inc. (ACSI) 1905 County Road C West Roseville, MN 55113 USA
Establishment Registration Number	3003477173
PMA Number	P110024
Date of Panel Recommendation	TBD
Date of FDA Notice of Approval	TBD
Expedited Status	FDA granted expedited review status on July 11, 2011

II. INDICATIONS FOR USE

The ResQCPR System is intended for use in the performance of CPR to increase survival with favorable neurologic function in patients with non-traumatic cardiac arrest.

III. CONTRAINDICATIONS

None known.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the ResQCPR System labeling (Instructions for Use).

V. DEVICE DESCRIPTION

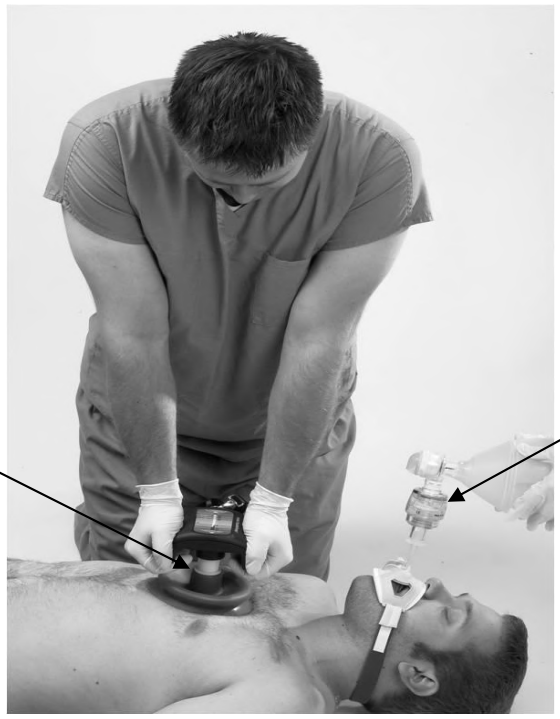
The ResQCPR System is a manual cardiopulmonary (CPR) system that consists of two components: the ResQPUMP ACD-CPR Device and the ResQPOD ITD 16 (**Figure 1**). Active compression decompression CPR with the ResQPUMP transforms the human chest into an active bellows. The

ResQPOD ITD 16 acts to lower airway pressure, thereby reducing intrathoracic pressure by impedance of respiratory gases during the decompression phase of CPR. The ResQCPR System is designed to enhance venous return to the heart, increase cardiac output and increase blood flow to vital organs during CPR.

The ResQCPR System also assists rescuers with optimal performance of CPR by use of:

- an audible metronome to guide the chest compression rate (on ResQPUMP)
- a visual display of force applied during compression and decompression (on ResQPUMP)
- timing lights for timing ventilations at a rate of 10 per minute (on ResQPOD ITD 16)

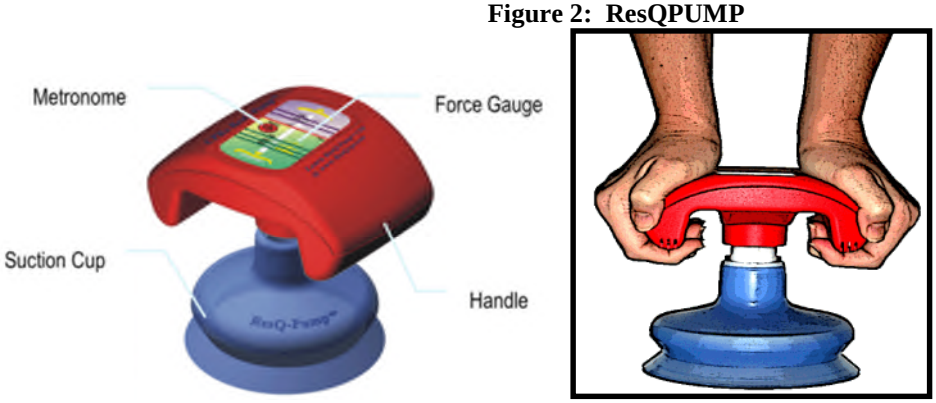
Figure 1: ResQCPR System- ResQPUMP and ResQPOD ITD 16



ResQPUMP ACD CPR Device

The ResQPUMP is a multi-use hand held ACD device that includes a suction cup for attachment to the skin over the mid-sternum, and a handle that the rescuer grasps during the performance of ResQCPR (**Figure 2**). The ResQPUMP assists the rescuer in compressing the chest during CPR and in actively lifting the chest upward during the decompression phase of CPR. The ResQPUMP handle includes a force gauge with a visual display of the forces exerted during chest compression and decompression. The force gauge has visual targets based on chest compliance as follows: 65 lbs of pressure for patients with softer compliance, 65-90 lbs for patients with average compliance, and 110 lbs for patients with stiffer compliance. When beginning ResQCPR, rescuers compress the chest approximately two inches with the ResQPUMP, observe the force depicted on the gauge and use that force as a guideline for continued ResQCPR compressions. Rescuers actively decompress the chest by lifting upwards to a targeted force indicated on the gauge of between -15 and -20 lbs, after each compression. The handle also includes a battery-powered audible metronome to guide timing of chest compressions at a rate of 80 compressions per minute.

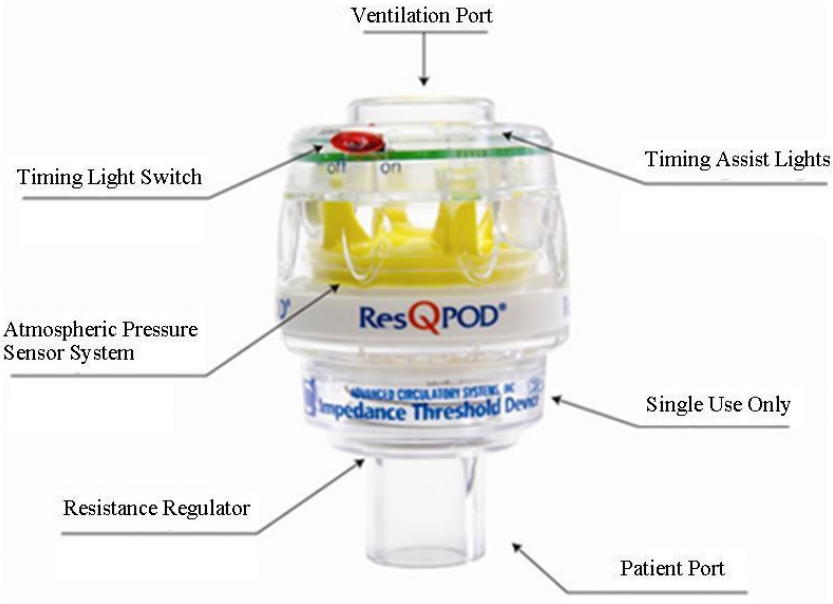
Figure 2: ResQPUMP



ResQPOD ITD 16 Impedance Threshold Device

The ResQPOD ITD 16 is a valve device that impedes air from entering the patient's thorax when pressures within the thorax are <0 atmospheres, and allows for positive pressure ventilation and expiration of respiratory gases with minimal resistance (<5 cm H_2O) (**Figure 3**). The ResQPOD ITD 16 has a secondary valve system with a resistance of -16 cm H_2O that opens when the pressure inside the thorax is < -16 cm H_2O, which may occur if the patient begins to breathe spontaneously. The ResQPOD ITD 16 fits on a face mask or advanced airway device and may be used with standard ventilation sources (either with or without supplemental oxygen supply), for example a bag-valve or demand-valve resuscitators, a rescuer's mouth, or an automated ventilator. Timing assist lights flash at a rate of 10 times per minute, thereby provide guidance to the rescuer on the proper ventilation rate during ResQCPR.

Figure 3: ResQPOD ITD 16



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no other devices cleared or approved for the same indications for use as the ResQCPR System. The alternative procedure is standard CPR, performed manually with a pair of hands or with an automated device. There are several automated CPR devices currently available on the market. These devices are generally indicated for use in performing external cardiac compressions. None of these automated devices are indicated to increase survival with favorable neurologic function in patients with non-traumatic cardiac arrest.

VII. MARKETING HISTORY

Marketing History of the ResQCPR System
The ResQCPR System, comprised of the ResQPUMP and ResQPOD ITD 16, has not been previously marketed as a System; however both components are currently marketed individually, as described below.

Marketing History of the ResQPOD ITD
Two models of the ResQPOD have been developed: the ResQPOD ITD 16 and the ResQPOD ITD 10. Both versions incorporate a check valve as a design safety feature in the event that the patient begins to breathe independently while the device is in place within the airway circuit. The ResQPOD ITD 16 is a component of the ResQCPR System, and includes a safety check valve that allows inspiration at -16 cm H_2O. The ResQPOD ITD 10 includes a safety check valve that allows inspiration at -10 cm H_2O. With the exception of the safety check valve resistance specification, the ResQPOD ITD 10 and ITD 16 are otherwise identical.

The ResQPOD ITD 10, also referred to as the ResQPOD Circulatory Enhancer, was cleared for marketing in the U.S. on June 11, 2003 via 510(k) (#K022906) and modified via 510(k) (#K033401) on November 20, 2003. It is intended for use in patients that may benefit from an increase in circulation, including spontaneously breathing patients and those receiving assisted ventilation. It is indicated for home, hospital, clinic and emergency care use, for the temporary increase in blood circulation as prescribed by a physician or licensed practitioner. The ResQPOD ITD 16 has been marketed outside the U.S. since 2003 and is indicated for use in the treatment of adult patients with cardiac arrest (absence of breathing and absence of circulation indicators).

The U.S. and foreign marketing clearance/approval history of both versions of the ResQPOD is shown in **Table 1**:

Table 1. Marketing History of ResQPOD ITD

	Date of Approval or Clearance	
Country	**ResQPOD ITD 10**	**ResQPOD ITD 16**
Australia		April 2009
Canada		December 2002
European Union		December 2002
Israel		May 2011
Japan		June 2011
South Korea	August 2009	
Turkey		June 2010
United States	June 2003	

The ResQPOD ITD 16 and ITD 10 have not been withdrawn from marketing for any reason related to the safety and effectiveness of the devices. There have been no reported adverse events resulting in clinical injury during commercial use of the ResQPOD ITD 16. There has been one reported adverse experience with the ResQPOD ITD 10 in 2007 (MDR Report Key #958271) related to the product packaging.

Marketing History of the ResQPUMP/CardioPump®

The ResQPUMP was originally designed and developed by Ambu Inc. (Ballerup, Denmark). Outside the U.S., the device is called the CardioPump. Two models of the CardioPump are currently commercially available outside the U.S.: one model has the same audible metronome as the ResQPUMP to guide rescuers in the proper rate of compressions/decompressions. The other model of the CardioPump does not have an audible metronome. The design of the CardioPump is identical to the ResQPUMP in all other aspects except that the force gauge mechanism label is displayed in kilograms on the CardioPump (force is displayed in lbs on the ResQPUMP).

Ambu began to manufacture and sell the CardioPump in 1992. Ambu also manufactured the ResQPUMPs used in the U.S. clinical trial until 2007, at which time Advanced Circulatory Systems, Inc. took ownership of the product, including manufacturing.

Advanced Circulatory obtained its own CE mark for the CardioPump on December 17, 2008, as a Class Im (measuring) device, subsequent to taking over ownership of the product from Ambu. Advanced Circulatory Systems, Inc. has marketed the CardioPump outside the U.S. since 2008, with an indication for use in the treatment of adult patients with out-of-hospital cardiac arrest (absence of effective pulse and respiration) to improve the overall efficiency of CPR and the chances for short and long term survival.

The foreign marketing approval history of the CardioPump (with Advanced Circulatory as the manufacturer) is shown in **Table 2**:

Table 2. Marketing History of the ResQPUMP/CardioPump

Country	CardioPump Approval Date
Australia	February 2009
Canada	December 2008
European Union	December 2008
Israel	May 2011
Turkey	December 2008

The CardioPump has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device. There have been no reported adverse events resulting in clinical injury during commercial use of the CardioPump.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Death remains the most common outcome for patients who experience a cardiac arrest, especially those occurring outside the hospital where time to treatment is a critical co-variable. The mortality rate for cardiac arrest patients remains extraordinarily high. Nationally, survival with favorable neurological function for all patients following OHCA and treated with S-CPR averages <6% (range from <1% to 20% nationwide).[1] Potential adverse effects of the ResQCPR System and the individual ResQPUMP and

ResQPOD ITD 16 components of the System have been evaluated in non-clinical and clinical studies. Observed adverse effects were primarily associated with improper use of the devices; that is, when the instructions for use (IFU) were not followed. For example, improper use of the ResQPUMP may potentially result in injuries, similar to those observed with improper performance of standard manual CPR. Applying excessive downward force may potentially break the ribs and/or the sternum, and may potentially result in internal organ laceration. The force gauge on the ResQPUMP provides guidance to the rescuer to reduce the risk of excessive downward forces while concurrently providing guidance on the appropriate amount of downward force needed to indirectly propel blood forward from the heart to the brain and other organs.

In the U.S. pivotal clinical trial (called the ResQTrial), there was no difference in the overall major adverse event rates between the study groups (p=0.043). The only difference in adverse events was an increase in pulmonary edema in the ResQCPR group which did not affect survival to hospital discharge with good neurological function.

Potential adverse events that may be associated with use of the ResQCPR System are similar to those associated with standard CPR, including but not limited to the following:

- Aspiration
- Bleeding, major (requiring intervention)
- Cardiac tamponade
- Cerebrovascular accident/cerebral bleeding
- Death
- Hemothorax
- Internal organ injury
- Pneumothorax
- Pulmonary edema
- Re-arrest
- Rib fracture
- Seizure
- Sternal fracture

Side Effects
Bruising and soreness of the chest is common following performance of any method of CPR, including CPR with the ResQCPR System. Proper positioning and compression depth during use of the ResQPUMP component may minimize the risk of causing such injuries.

IX. SUMMARY OF NON-CLINICAL STUDIES

Laboratory Studies
Bench studies were performed to assess the relevant structural and functional components of the ResQPUMP and ResQPOD ITD 16 devices and to confirm their compliance with applicable specifications and standards. Critical testing for the ResQPUMP included: force gauge calibration and measurement, metronome verification (tone frequency and sound intensity), software verification, operating and storage temperature extremes, suction cup attachment and release forces, battery service/shelf life, biocompatibility, electromagnetic compatibility, and mechanical shock (drop testing). Critical testing for the ResQPOD ITD 16 included: expiratory and inspiratory airway impedance, air flow/loss, operating and storage temperature extremes, timing assist light functionality, accelerated aging, biocompatibility, electromagnetic compatibility, and mechanical shock (drop testing). Both devices passed all relevant structural and functional bench testing requirements.

Animal Studies

Studies have been performed as part of prior research efforts to elucidate the physiologic mechanism of action of the ResQCPR System and to confirm the performance of ResQCPR in animal models of cardiac arrest.[2-6] Based on the prior non-clinical and clinical experience (described below) using the ResQPUMP and ResQPOD ITD 16 individually or in combination, additional pre-clinical animal studies were not required as part of the product development and design verification of the ResQCPR System prior to conducting the U.S. clinical ResQTrial.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The ResQTrial, the clinical study that formed the basis for the finding that the ResQCPR System is safe and effective for its intended use, was a prospective, multi-center, two-arm, randomized, controlled, partially masked clinical study.[7] The study included a run-in phase and a pivotal phase. Clinical protocol requirements, including patient selection criteria and randomization to study treatment arms, were the same in both phases. The study was conducted under 21 C.F.R. §50.24, *Exemption from Informed Consent under Emergency Circumstances*, and was funded by a grant from the National Institutes of Health (NIH).

Major Study Design Characteristics

The ResQTrial was designed to compare standard manual closed-chest CPR (S-CPR), the current standard of care for patients in cardiac arrest, with ResQCPR in subjects with an out-of-hospital cardiac arrest of presumed cardiac etiology. Subjects were provisionally enrolled to receive S-CPR (the control group) or ResQCPR (also called ACD+ITD). A prospective, computer-generated, block randomization weekly schedule was used. Subjects were assigned to CPR treatment groups on a 1:1 ratio. Apart from the rescuer CPR, all other aspects of the study, including obtaining the subject's consent for continued participation in the study and administration of neurologic assessments, were performed by research staff masked to the CPR treatment assignment.

The primary study objective was to compare S-CPR with ResQCPR. The original study design also included a third group of subjects that were randomly assigned to S-CPR plus the ResQPOD ITD 16 alone (S-CPR+ITD). The S-CPR+ITD study arm was discontinued in November 2007 because of slower than expected overall enrollment and an intention to focus remaining funding resources on collection of data in the two primary study groups of interest.

The ResQTrial was conducted in seven study sites at distinct geographic locations in the U.S. These sites included 46 EMS agencies in urban, suburban and rural areas, encompassing a total population of approximately 2.3 million. Approximately 5000 EMS personnel received initial training and routine refresher training on the study CPR procedures throughout the course of the study. A total of 40 hospitals participated in the care of the subjects.

The study included a run-in phase that was required to be completed at all sites prior to beginning enrollment in the pivotal phase (**Table 3**). Enrollment in the run-in phase began in October 2005 and ended in April 2009 at the last participating site. Subjects were enrolled in the pivotal phase from March 2006 to July 2009, and one-year follow-up was completed for the final subject in July 2010.

Table 3: Characteristics of the ResQTrial[1]

Study Phase	Design	Purpose	#of Study Sites	Subjects Randomized to S-CPR	Subjects Randomized to ResQCPR
Run-in Phase	Multi-center, prospective, randomized, controlled, partially- masked clinical trial	Confirm that sites were able to successfully execute all aspects of the study protocol prior to beginning enrollment in the pivotal phase	7	134 randomized 90 met mITT criteria: 9 were discharged alive; of these, 0 withdrew or were lost to follow-up by one year; 3 had died.	134 randomized 98 met mITT criteria: 12 were discharged alive; of these, 2 withdrew or were lost to follow-up by one year; 1 had died.
Pivotal Phase	Multi-center, prospective, randomized, controlled, partially-masked clinical trial	Evaluate the safety and effectiveness of the ResQCPR System	7	1201 randomized 813 met mITT criteria: 80 were discharged alive; of these, 13 withdrew or were lost to follow-up by one year; 19 had died.	1269 randomized 842 mITT criteria: 105 were discharged alive; of these, 18 withdrew or were lost to follow-up by one year; 13 had died.

[1] Subjects enrolled in the pivotal phase, randomized to S-CPR or ResQCPR, and who met the modified intention to treat (mITT) criteria constituted the primary analysis population. Subjects enrolled in the pivotal phase and randomized to S-CPR or ResQCPR constituted the intention-to-treat (ITT) analysis population.

Given the emergency nature of the setting for conducting the trial and anticipated poor outcomes in the majority of enrolled subjects, a randomized clinical trial design with carefully pre-defined analysis populations was used in order to collect the most scientifically sound data while also reducing the potential for bias. On-scene CPR personnel could not be blinded to the randomized CPR method used; however, all other study personnel (e.g., Company, investigators and their research staff, independent CEC) were blinded to the study results by group assignment until completion of enrollment and required follow-up at one year. The independent DSMB was blinded to the study results by group assignment until they requested to be unblinded in July 2009. Randomization according to a weekly schedule (by physically placing and removing study devices on emergency vehicles each week) was undertaken to facilitate and manage study equipment and communications to the rescue personnel, to reduce the potential for subject selection bias, and to reduce the likelihood of randomization errors.

Device Design Changes During the Study

The ResQPOD ITD 16 includes timing lights for guidance in providing ventilations at the recommended rate during CPR. The original (version 1) ResQPOD ITD 16 included timing lights that flashed at the rate of 12/minute, in accordance with the American Heart Association CPR guidelines recommendation for ventilation rate at that time. Six months after the start of the study, the CPR guidelines were revised to recommend a slower ventilation rate of 8-10 breaths/minute. Following the revised recommendation, a design change was made to the ResQPOD ITD 16 to reduce the timing light rate to 10 flashes per minute (version 2). The design change did not affect the primary inspiratory impedance function of the ResQPOD ITD 16. In the pivotal study phase, version 1 was used in only 1.1% of enrolled subjects. In consideration of the low usage rate of version 1, poolability of clinical results using both versions of the ResQPOD ITD 16 is justified.

Clinical Endpoints

The primary safety and effectiveness endpoint was survival to hospital discharge with favorable neurologic function, defined as a modified Rankin Scale score (MRS) of ≤ 3. The MRS was selected because this assessment takes into consideration the subject's neurologic status both prior to and following cardiac arrest. MRS is evaluated on a scale of 0-6, with 0 representing no impairment and 6 representing death. The secondary safety endpoint was the overall rate of major adverse events through hospital discharge. The secondary effectiveness endpoint was long term neurologic function assessed using the Cognitive Abilities Screening Instrument (CASI, Version E-1.1). CASI was selected because it is a validated instrument for screening cognitive impairment. CASI is measured on a scale of 0-100, with higher scores signifying better outcomes. Other secondary endpoints included return of spontaneous circulation (ROSC) assessed out-of-hospital and in-hospital, as applicable, and survival to hospital admission, 30 days, 90 days and 1 year after cardiac arrest. MRS, CASI and other secondary endpoints of neurologic recovery and psychological status were assessed as shown in **Table 4.**

Table 4: Follow-Up Neurologic Assessment Tools and Schedule

Assessment Tool	**Hospital Discharge** up to 5 days after discharge	**30-day Survival** within 30+/- 5 days	**90-day Survival** within 90 +/- 5 days	**1-year Survival** within 365 +/- 15 days
Modified Rankin Scale (MRS)	X (1° endpoint)			
Cerebral Performance Category (CPC)/ Overall Performance Category (OPC)	X	X	X	X
Secondary Endpoint Assessment Tools				
Health Utilities Index 3 (HUI3)	X	X	X	X
Disability Rating Scale (DRS)		X	X	X
Cognitive Abilities Screening Instrument (CASI)			X	X
Trail-Making Test (TMT)			X	X
Beck Depression Inventory II (BDI-II)			X	X
Mayo-Portland Adaptability Inventory-4 (MPAI-4)			X	
Quality of Life Survey (QOLS)				X

Success/Failure Criteria

It is well established that subjects in cardiac arrest represent a heterogeneous population: some individuals are known to respond well to CPR while others respond poorly to CPR with little or no likelihood of survival with any treatment.[1,8] Therefore, the ResQTrial focused on subjects who have the capacity to benefit from CPR, which is why the study used a modified intention-to-treat (mITT) primary analysis population. Subjects were included in the mITT population based on the criteria listed in the Clinical Inclusion and Exclusion Criteria section below.

Individual patient success was defined as achievement of the primary composite endpoint (survival to hospital discharge with an MRS score ≤3). Overall study success was defined as a statistically significant increase in rate of primary endpoint achievement in the ResQCPR group over S-CPR, in the primary mITT analysis population.

Statistical Analysis Plan

The primary study analyses were conducted on the population of subjects randomized to S-CPR or ResQCPR, and who met the criteria for the mITT population. Supplemental analyses were also performed in the intention-to-treat (ITT) population of subjects randomized to S-CPR or ResQCPR, and who met the initial enrollment criteria for the study.

The study was designed to test the hypothesis that treatment with the ResQCPR System results in increased survival to hospital discharge with favorable neurologic function, compared with S-CPR treatment, for subjects who meet the mITT criteria. The primary composite endpoint, survival to hospital discharge with an MRS score ≤3, was evaluated using Fisher's Exact Test of the equality of proportions between study arms. The secondary safety endpoint, rate of major adverse events, was evaluated at study completion using an exact, binomial test of the non-inferiority of the rate of major adverse events in the ResQCPR group compared with the S-CPR group. The secondary effectiveness endpoint was long term neurological function, evaluated in superiority tests of mean Cognitive Abilities Screening Instrument (CASI) scores using a two-group Student's t-test. CASI outcomes were assessed according to a hierarchical closed test procedure (first at 90 days, then repeated at one year). For subjects who survived until discharge, but who died prior to the 90-day or one-year evaluation, a CASI score of zero was

assumed. No imputed data were used for analyzing the primary endpoint or the secondary safety endpoint.

Sample Size Justification

On the basis of an expected 6.0% rate for achievement of the primary endpoint in the S-CPR group, and 10.2% in the ResQCPR group, a sample size of 700 mITT subjects per group was projected to detect a significant improvement with a final significance level of 0.049 with 80% statistical power. The 6% rate was based upon the known survival rates in the clinical tests sites and the hypothesized benefit was based upon prior animal and clinical studies.[9-12] A study mid-point interim analysis was prospectively planned for purposes of upward sample size adjustment, if warranted. The final significance level requirement of 0.049 reflected an adjustment for this interim analysis based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

The original study plan called for 700 mITT subjects per treatment arm in the pivotal phase. A single pre-planned midpoint interim analysis after enrolling 350 mITT subjects per arm occurred in March 2008. The Company, investigators, and DSMB were blinded to the treatment groups at this time. Based upon this interim analysis, a sample size increase to 1348 subjects per arm was recommended by the DSMB to maintain a statistical power of 80%. Two additional study sites were added to increase the enrollment rate. The seventh and last study site began enrollment in the pivotal phase in April 2009.

Early Study Termination

Efforts to obtain continued funding through the NIH to enroll the full 1348 subjects per study arm were undertaken but ultimately not successful. In July 2009, the DSMB recommended that new subject enrollment be curtailed if there was insufficient funding to enroll the proposed full number of additional subjects so as to not unnecessarily involve subjects in an investigational research study that could not be fully funded. The study was terminated in July 2010 due to this lack of funding. A total of 1655 mITT subjects were ultimately enrolled by the time of study discontinuation.

External Evaluation Groups

During the course of the study, an independent 3-person Clinical Events Committee (CEC) met, reviewed all adverse events, and determined, in a blinded manner, whether cases selected by the site investigators for review met criteria for the mITT analysis population. Also during the study, a 7-person independent Data Safety Monitoring Board (DSMB) that included a member appointed by NIH reviewed all aggregate data in a blinded manner to assure the study was performed in the best interests of the public and the subjects and provide recommendations whether or not to continue subject enrollment. The composition of these external evaluation groups remained the same throughout the study.

Clinical Inclusion and Exclusion Criteria

Enrollment was limited to subjects who met the selection criteria listed in **Table 5.**

Table 5: ResQTrial Selection Criteria

Initial Inclusion Criteria	Initial Exclusion Criteria
Adult subjects initially presumed or known to be 18 years of age or older	Subjects initially presumed or known to be < 18 years of age
Subjects who present with presumed non-traumatic, out-of-hospital cardiac arrest and who are candidates for resuscitation attempts	Subjects with obvious or likely traumatic injuries causing cardiac arrest
	Subjects with pre-existing do-not-resuscitate (DNR) orders
	Subjects with signs of obvious clinical death or conditions that preclude use of CPR
	Subjects whose family or legal guardians request that the subject not be entered in the study at the time of arrest
	Subjects experiencing in-hospital cardiac arrest Recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known
mITT Inclusion Criteria	**mITT Exclusion Criteria**
Adult subjects initially presumed or known to be 18 years of age or older	Adult subjects presumed or known to be < 18 years of age
Subjects who present with out-of-hospital cardiac arrest from presumed cardiac etiology and who receive CPR by emergency medical services (EMS) personnel for at least one minute	Subjects with known or likely traumatic injuries causing cardiac arrest or cardiac arrest of presumed non-cardiac origin including subjects with metabolic abnormalities or drug overdose
Subjects whose airways are managed with a cuffed endotracheal tube, Combitube or laryngeal mask airway or facemask	Subjects with pre-existing DNR orders
	Subjects with signs of obvious clinical death or conditions that preclude use of CPR
	Family or legal representative request that the subject not be entered into the study
	Subjects experiencing in-hospital cardiac arrest
	Subjects with a recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known)
	Subjects who received less than one minute of CPR by EMS personnel
	Subjects with a complete airway obstruction that cannot be cleared or in whom attempts at advanced airway management are unsuccessful
	Subjects intubated with a leaky or uncuffed advanced airway device or presence of stomas, tracheotomies or tracheostomies
	Subjects who re-arrest and are encountered by EMS within 365 days of the index cardiac arrest

Treatment and Follow-Up Protocols

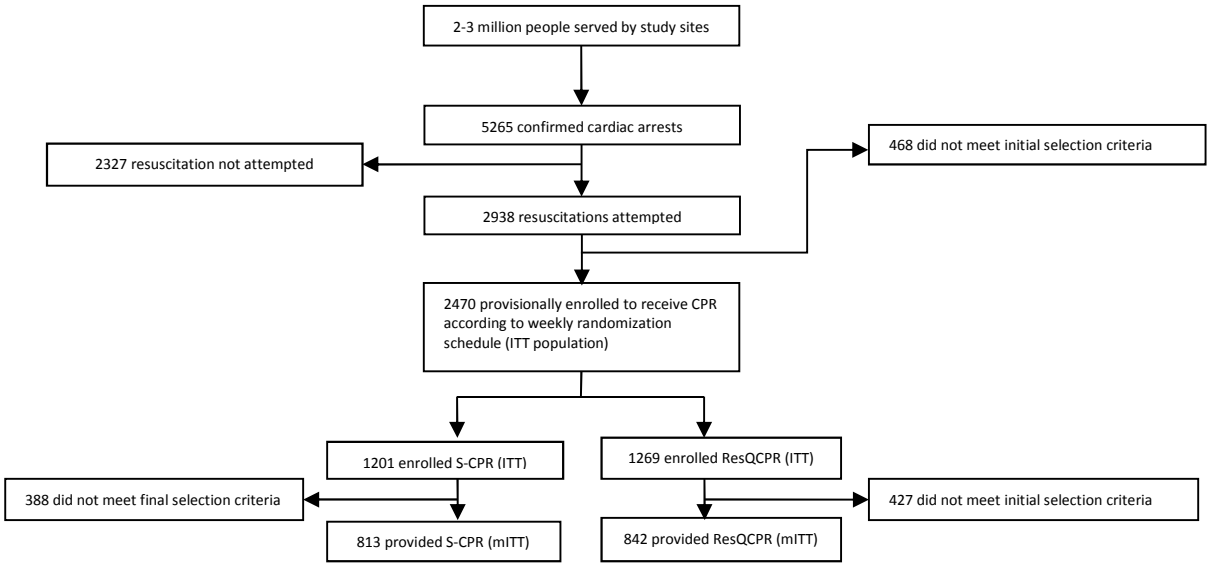
The first basic or advanced life support EMS provider to arrive started chest compressions as soon as possible for both study groups. Standard CPR, defibrillation, and advanced life support treatment were performed in accordance with local and national policies and procedures. The compression to ventilation ratio was 30:2 during basic life support for both CPR techniques. Rescuers provided ResQCPR at 80 compressions per minute as soon as possible, using the ResQPUMP force gauge to guide the recommended compression depth and complete chest recoil. Rescuers initially attached the ResQPOD ITD 16 between the ventilation bag and facemask, and subsequently relocated it to the advanced airway. The ResQPOD ITD 16 was removed and ResQCPR was stopped if the subject had ROSC, and initiated again if re-arrest occurred. CPR efforts in both groups were encouraged for at least 30 minutes on scene before the resuscitation attempt was stopped. In-hospital therapeutic hypothermia and coronary

revascularization for all applicable subjects were encouraged but not part of the formal protocol. Follow-up was performed as summarized in **Table 4**.

Accountability of the PMA Cohort

At the time of database lock, 110 (6.6 %) of the 1655 subjects enrolled in the pivotal phase, and who met the final selection criteria (mITT), were alive and available for analysis at their completion of the study (one year follow-up). Accountability for all subjects enrolled in the pivotal phase and randomized to treatment with S-CPR or ResQCPR is shown in **Figure 4**.

Figure 4: ResQTrial Pivotal Phase- Subject Accountability in S-CPR and ResQCPR Study Groups



Study Population Demographics and Baseline Parameters

Demographics and baseline characteristics were balanced between the study groups (**Table 6)**.

Table 6: ResQTrial Pivotal Phase- Demographics and Baseline Characteristics[1]

Parameter	mITT		ITT	
	S-CPR (n=813)	**ResQCPR (n=842)**	**S-CPR (n=1201)**	**ResQCPR (n=1269)**
Age, years (mean ± SD)	66.8 ± 14.5	67.0 ± 15.2	64.2 ± 17.2	63.3 ± 17.8
Male	539 (66.3)	559 (66.4)	752 (62.6)	803 (63.3)
Race:				
White	660 (81.2)	715 (84.9)	960 (79.9)	1035 (81.6)
Asian	31 (3.8)	19 (2.3)	39 (3.2)	29 (2.3)
Native Hawaiian/ Pacific Islander	3 (0.4)	1 (0.1)	4 (0.3)	1 (0.1)
American Indian/Alaska Native	9 (1.1)	10 (1.2)	18 (1.5)	22 (1.7)
Black/African American	94 (11.6)	88 (10.5)	152 (12.7)	155 (12.2)
Unknown	16 (2.0)	9 (1.1)	28 (2.3)	26 (2.1)
Ethnicity:				
Hispanic/Latino	15 (1.8)	19 (2.3)	22 (1.8)	32 (2.5)
Not Hispanic/Latino	782 (96.2)	811 (96.3)	1149 (95.7)	1207 (95.2)
Unknown	16 (2.0)	12 (1.4)	30 (2.5)	29 (2.3)
Bystander witnessed arrest	383 (47.1)	400 (47.5)	517 (43.1)	546 (43.2)
EMS witnessed arrest	76 (9.4)	80 (9.5)	146 (12.2)	144 (11.4)
Unwitnessed arrest	353 (43.4)	361 (42.9)	536 (44.7)	575 (45.5)
Not available	1	1	2	4
Bystander CPR	350 (43.1)	358 (42.5)	489 (40.7)	532 (42.0)
Not available	1 (0.1)	0 (0.0)	1	2
Initial recorded cardiac rhythm:				
Ventricular fibrillation/pulseless ventricular tachycardia	247 (30.4)	292 (34.7)	294 (24.5)	335 (26.4)
Asystole	379 (46.6)	376 (44.7)	597 (49.7)	633 (49.9)
Pulseless electrical activity	180 (22.1)	171 (20.3)	293 (24.4)	284 (22.4)
Not available	7 (0.9)	3 (0.4)	17	16
911 call to EMS CPR start, minutes[2](mean ± SD)	6.6 ± 3.4	6.7 ± 3.2	6.7 ± 3.5	6.7 ± 3.2
911-to-first study device placed, minutes (mean ± SD)[2]	-	7.1 ± 3.5	-	7.1 ± 3.5
Duration CPR, minutes (mean ± SD)	27.60 ± 12.24	28.10 ± 11.45	25.6 ± 13.0	26.3 ± 12.3
Pre-hospital ROSC[3]	324 (39.9)	345 (41.0)	490 (40.8)	524 (41.3)

[1]Numbers shown are subjects (%)
[2]Does not include subjects with EMS witnessed arrests
[3] ROSC= Return of spontaneous circulation

Safety and Effectiveness Results

Primary Composite Safety and Effectiveness Endpoint

The primary endpoint analysis was based on the 1655 evaluable subjects (mITT) up to the time of hospital discharge. Subjects treated with ResQCPR had a 52% relative increase in survival to hospital discharge with an MRS ≤3 (primary endpoint): 8.9% (75 subjects) vs. 5.9% (47 subjects); p=0.019, OR 1.58 [CI= 1.06, 2.35]. Therefore, the study met the primary endpoint. There were no survivors with favorable neurologic function in either group if CPR was initiated >10 minutes after the 911 call. At one year, there was a 49% increase in survival in the ResQCPR group: 9.0% (74 subjects) versus 6.0% (48 subjects) in the S-CPR group; p=0.030. Neurologic function was similar between groups at 3 months and one year after cardiac arrest. There was no increase in the number of subjects with severe neurologic impairment in the ResQCPR group.

An analysis of all subjects randomized and treated in the pivotal phase of the ResQTrial with known primary endpoint data (the ITT population) revealed that 71/1186 (6.0%) treated with S-CPR survived to hospital discharge with a MRS ≤3 compared with 101/1262 (8.0%) in the ResQCPR group (OR 1.37; 95% CI [0.99, 1.90]; p=0.057).

Key effectiveness endpoints in the mITT and ITT analysis populations are summarized in **Table 7**. There was a 52% increase in survival to hospital discharge with favorable neurologic function (primary study endpoint) in subjects with an OHCA of presumed cardiac etiology (mITT population) treated with the ResQCPR System (75/838) compared with S-CPR (47/800) (p=0.019). The adverse events rates were similar between groups. One year after OHCA, there were 49% more subjects alive in the ResQCPR group and the vast majority of surviving subjects in both treatment groups had excellent neurological function.

Table 7: ResQTrial Pivotal Phase- Principal Safety and Effectiveness Results through One Year[1]

Parameter	mITT			ITT		
	S-CPR (n=813)	**ResQCPR (n=842)**	**p-value**	**S-CPR (n=1201)**	**ResQCPR (n=1269)**	**p-value**
In-Hospital Survival and Neurologic Outcomes						
Admitted to hospital	216 (26.6)	239 (28.4)	0.409	342 (28.5)	381 (30.0)	0.401
Survival to 24 hours Not available	176 (21.9) 9	199 (23.8) 6	0.378	277 (23.1) 12	310 (24.4) 11	0.701
Survival to hospital discharge Not alive at hospital discharge Not available	80 (9.9) 727 6	105 (12.5) 735 2	0.118	123 (10.2) 1072 6	150 (11.8) 1114 5	0.428
MRS $\leq$ 3 at discharge **(Primary Endpoint)**	47 (5.9)	75 (8.9)	0.019	71 (5.9)	101 (8.0)	0.057
Subjects with $\geq$1 major adverse event through hospital discharge **(Secondary Safety Endpoint)**[2]	766 (94.2)	789 (93.7)	0.681	1129 (94.0)	1194 (94.1)	0.932
Survival and Neurologic Outcomes at 90 days						
Alive at 90 days Not alive at 90 days Not available	58 (7.3) 740 15	87 (10.4) 746 9	0.029	88 (7.3) 1089 24	116 (9.1) 1129 24	0.108
CASI (mean ± SD) (**Secondary Effectiveness Endpoint)**[3]	69.86 ± 41.69	74.38 ± 37.48	0.549	69.65 ± 41.11	73.28 ± 38.20	0.584
Survival and Neurologic Outcomes at 12 Months						
Alive at 1 year Not alive at 1 year Not available	48 (6.0) 746 19	74 (9.0) 748 20	0.030	68 (5.7) 1103 30	96 (7.6) 1137 36	0.062
CASI (mean ± SD)[3]	57.39 ± 47.04	71.89 ± 41.04	0.100	53.42 ± 46.80	62.83 ± 44.52	0.215

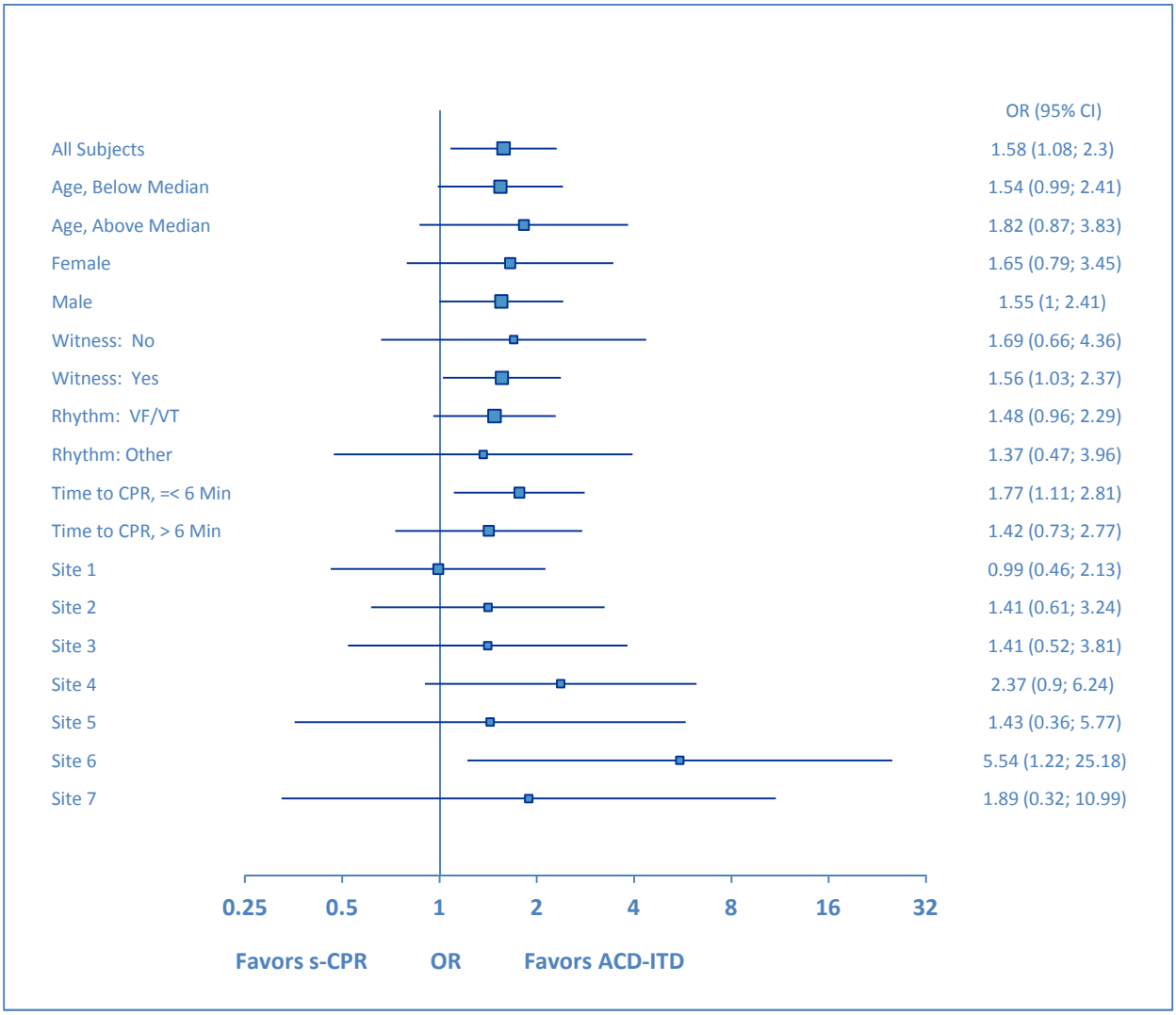
[1]Data shown are number of subjects (%) unless otherwise noted. Survival percentages are based on number of subjects with known survival status. P values and percentages were calculated based on the number of subjects with known status at each follow-up interval. Abbreviations: MRS – Modified Rankin Scale, scale is 0-6 where 0=no symptoms and 6=dead; CASI – Cognitive Abilities Screening Instrument, scale is 0-100 where 100=no impairment and 0=severe impairment;

[2]Major adverse events include: death, re-arrest, pulmonary edema, seizure, bleeding requiring intervention, rib/sternal fractures, pneumothorax, hemothorax, cardiac tamponade, CVA, aspiration, and internal organ injury.

[3]CASI score of 0 assigned to subjects who survived to hospital discharge but died prior to follow-up

Primary endpoint results were consistent across study sites, subject age groups, and gender (**Figure 5)**. There were nearly twice as many male subjects in the study as females, consistent with the known difference in frequency of cardiac arrest between genders. In both groups, males had a higher survival rate. The increase in male survivors with an MRS ≤3 was greater in the ResQCPR group versus the S-CPR group [OR 1.55, (CI =1.00, 2.40)]. Subjects in the ResQCPR group with a witnessed arrest had a greater likelihood of survival with an MRS ≤3, compared with the S-CPR group [OR 1.56 (CI= 1.03, 2.37)].

Figure 5: ResQTrial Pivotal Phase- Effects of Age, Study Site, Gender, and Study CPR Treatment on Primary Endpoint (mITT). Estimated odds ratios (OR) exceeded 1.00 (e.g., favored ACD-ITD) for subgroups based on age (median age was 67 years, interquartile range 56-79), gender, witnessed status, time to CPR start, and all study sites except site 1. VF/VT= ventricular fibrillation and pulseless ventricular tachycardia.



Secondary Safety Endpoint

The primary analysis of safety was based on the randomized cohort of 1655 subjects (mITT) available for the evaluation prior to hospital discharge. The safety analysis included major adverse events that were reported during the pre-hospital resuscitation effort and up to the point of hospital discharge, as applicable. There were no differences in overall major adverse event rates between the study groups; thus

the secondary safety endpoint was met. Similar findings were observed in the ITT analysis population. The overall secondary safety endpoint results and survival to hospital discharge, 30 days, 90 days and one year following cardiac arrest are shown in **Table 7**.

Reported major adverse events by type are shown in **Table 8**. The only statistically significant difference in adverse events between the two groups was the observation that more patients treated with ResQCPR had pulmonary edema. A post hoc analysis demonstrated that the presence of pulmonary edema did not adversely affect survival to hospital discharge with a mRS≤3, the primary study endpoint.

Table 8: ResQTrial- Subjects with Major Adverse Events through Hospital Discharge[1]

Event	mITT			ITT		
	S-CPR (n=813)	ResQCPR (n=842)	P value	S-CPR (n= 1201)	ResQCPR (n= 1269)	P value
Subjects with ≥1 major adverse event through hospital discharge (secondary safety endpoint[2])	766 (94.2)	789 (93.7)	0.681	1129 (94.0)	1194 (94.1)	0.932
Death	729 (89.7)	735 (87.3)	0.144	1074 (89.4)	1115 (87.9)	0.229
Re-arrest	161 (19.8)	185 (22.0)	0.304	230 (19.2)	260 (20.5)	0.420
Stroke/cerebral bleeding	3 (0.4)	2 (0.2)	0.682	11 (0.9)	11 (0.9)	1.000
Internal organ injury	0 (0.0)	1 (0.1)	1.000	2 (0.2)	2 (0.2)	1.000
Hemothorax	1(0.1)	2 (0.2)	1.000	3 (0.3)	3 (0.2)	1.000
Bleeding requiring intervention	3 (0.4)	7 (0.8)	0.343	8 (0.7)	17 (1.3)	0.109
Cardiac tamponade	3 (0.4)	2 (0.2)	0.682	4 (0.3)	5 (0.4)	1.000
Aspiration	7 (0.9)	8 (1.0)	1.000	20 (1.7)	16 (1.3)	0.408
Pneumothorax	7 (0.9)	10 (1.2)	0.628	11 (0.9)	13 (1.0)	0.840
Seizure	13 (1.6)	11 (1.3)	0.684	19 (1.6)	23 (1.8)	0.349
Rib/Sternal fracture	14 (1.7)	11 (1.3)	0.549	23 (1.9)	18 (1.4)	0.349
Pulmonary edema[3]	62 (7.6)	94 (11.2)	0.015	96 (8.0)	143 (11.3)	0.006

[1] Numbers shown are subjects with at least one report of the listed adverse event types. If multiple events of same type were reported, the event is only counted once per subject. Reports of deaths, re-arrest, seizure, and pulmonary edema in the field (e.g., pre-hospital) are also shown. All other adverse event types were assessed based on review of medical records for subjects transported to a hospital. There were no Major Adverse Events associated with device malfunctions, defects, or failures.

[2] Secondary safety endpoint: The rate of major adverse events in the ResQCPR group (mITT) was found to be non-inferior to that in S-CPR group ($p < 0.0001$) within a non-inferiority margin of 5%.

[3] Data shown includes combined pre-hospital and in-hospital reports of pulmonary edema. Pulmonary edema was defined as any of the following: *Pre-hospital reports* of advanced airway filled with fluid ≥2 times; blood, mucous, fluid or other secretions in the airway; reports of pulmonary edema or pleural/pulmonary effusion on post-mortem examinations; and, for subjects transported to a hospital, *in-hospital reports* of pulmonary edema or pleural/pulmonary effusion confirmed on x-ray or CT scan. Pre-hospital pulmonary edema was reported in 22 patients (2.7%) in the S-CPR group, and in 30 patients (3.6%) in the ResQCPR group (p= 0.328) (mITT).

Secondary CASI Effectiveness Endpoint

The pre-specified secondary effectiveness endpoint was an evaluation of long-term neurological function for subjects in the mITT population. Mean Cognitive Abilities Screening Instrument (CASI) Scores for patients receiving ResQCPR were hypothesized to be superior 90 days and 365 days after cardiac arrest when compared with subjects treated with S-CPR. While there was a statistically significant 49% increase in survival to 90 and 365 days after OHCA in the ResQCPR treatment arm compared with S-CPR ($p = 0.024$ and 0.030, respectively), mean 90 and 365 day CASI scores were not significantly different among survivors who were discharged from the hospital (p=0.549 and 0.100, respectively) as hypothesized. The mean scores included subjects who died after hospital discharge, with a CASI score

equal to 0 assigned to those who died. More than 85% of the one year survivors in both study arms completed the one year CASI assessment. The mean ± S.D. CASI scores for these subjects were 93.7 ± 11.8 (n=30) in the S-CPR arm and 94.7 ± 4.4 (n=41) in the ResQCPR arm (p=0.68), consistent with full or nearly full recovery in both groups. There were only three patients with CASI scores <70, a score consistent with poor neurological function, in both groups.

Survival

The number and percent of subjects that survived to hospital admission, 24 hours, hospital discharge, 90 days, and 1 year after the index cardiac arrest is shown in **Table 7**. At 1 year, there was a 49% increase in the survival rate in subjects in the mITT population treated with ResQCPR compared with S-CPR (p=0.030. There was a trend toward similar findings in the ITT analysis population.

Survival outcomes were evaluated using Kaplan-Meier actuarial analyses from the time of hospital discharge to one year after OHCA, with differences between treatment groups assessed for significance with Log Rank (Mantel-Cox) statistics (**Figure 6-mITT** and **Figure 7-ITT**). Survival information for at least 24 hours was available for 99.8% of all subjects.

Figure 6: Kaplan Meier Survival [all mITT subjects discharged alive]
[P= 0.033 (Log Rank (Mantel-Cox)] test of equality of survival distributions for the different levels of Group.

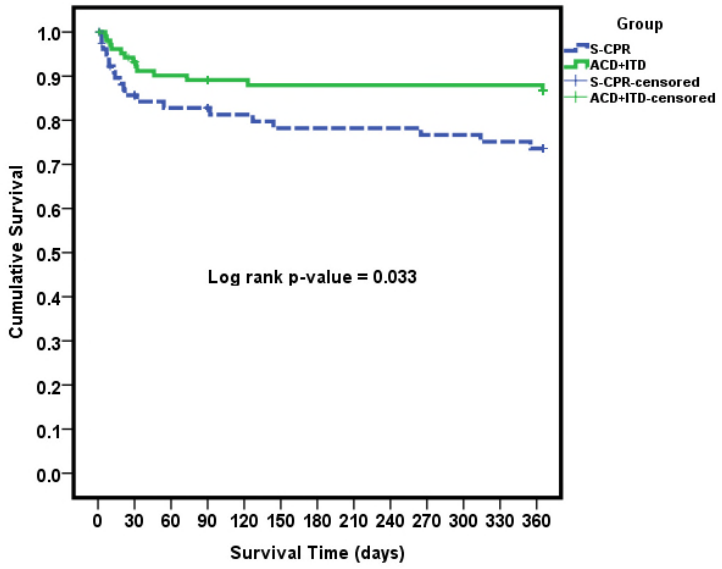
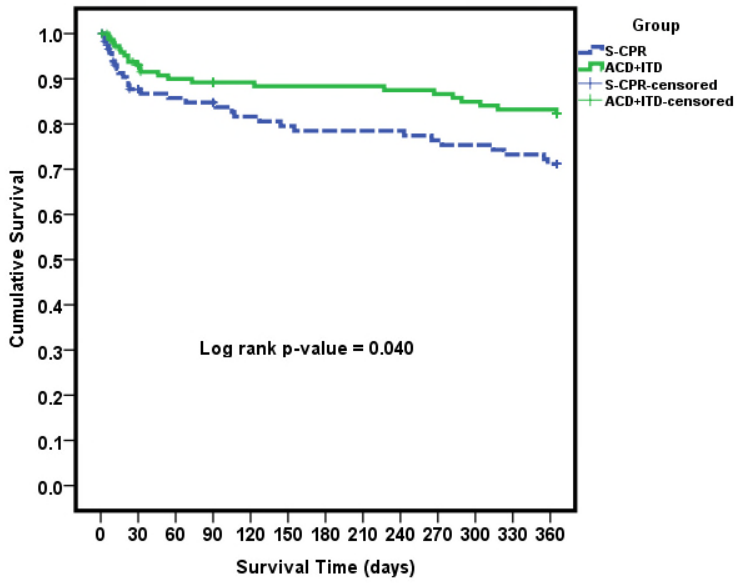


Figure 7: Kaplan Meier Survival [all ITT subjects discharged alive]
[P= 0.040 [Log Rank (Mantel-Cox)] test of equality of survival distributions for the different levels of Group.



Device Failures

Table 9: ResQTrial Pivotal Phase- ResQPOD ITD 16 and ResQPUMP Device Failures

	Device Failures mITT (n=842)	**Device Failures ITT (n=1269)**
ResQPOD ITD 16 Failure:		
timing lights for ventilation guidance did not work	60	87
male adaptor of bag/valve/mask broke off, lodged within device	1	1
difficult ventilation using device, unspecified	1	1
ResQPOD ITD 16 failure rate, overall	62/842 (7.4%)	90/1269 (7.1%)
ResQPOD ITD 16 failure adversely affecting patient care	0/842 (0%)	0
ResQPUMP Failure:		
force gauge	2	2
metronome	9	13
suction cup detachment	1	1
ResQPUMP failure rate, overall	12/842 (1.4%)	16/1269 (1.3%)
ResQPUMP failure adversely affecting patient care	0/842 (0%)	0

Other Neurologic Assessments

The secondary neurologic assessment endpoints were compared using nonparametric Mann-Whitney U tests. While there were more survivors in the ResQCPR group, among all survivors there were no differences between the study groups observed in these secondary endpoints (**Table 8**).

Table 10: Summary of Secondary Neurologic Assessment Endpoints at 12 months[1]

Neurologic Assessment	mITT		ITT	
	S-CPR	ResQCPR	S-CPR	ResQCPR
Health Utilities Index Mark 3(HUI3)	12.49±4.45	12.10±6.00	13.85±7.34	12.45±5.87
Disability Rating Scale (DRS)	1.39±3.12	2.19±5.68	2.46±5.47	2.91±6.09
Trail Making Test	49.56±43.37	47.10±27.26	48.95±41.69	50.96±32.54
Beck Depression Inventory (BDI)	5.23±6.29	5.46±5.93	6.52±7.25	5.87±6.04
Quality of Life	2.02±0.90	2.09±0.99	2.05±0.98	2.20±1.06

[1] Data shown are mean scores ± standard deviation

Additional Analyses

All Non-traumatic Arrest Subjects Enrolled in the ResQTrial. A total of 2738 subjects that met the study eligibility criteria were randomized to ResQCPR or S-CPR during the entire study, including the run-in phase. The neurological status at the time of hospital discharge was known in 2714 (99.1%) of these subjects. In the ITT analysis population including the combined run-in and pivotal phases, 7.9% (110/1396) of those randomized to ResQCPR treatment achieved the primary endpoint, versus 5.7% (75/1318) of those randomized to S-CPR (p-value= 0.027). In the mITT analysis population including the combined run-in and pivotal phases, 9.0% (84/936) of subjects randomized to ResQCPR treatment achieved the primary endpoint, versus 5.6% (50/899) of those randomized to S-CPR (p-value= 0.005).

Overall Conclusions

The results of the pivotal trial show that the effect of the ResQCPR System on survival to hospital discharge with favorable neurologic function is superior to conventional manual S-CPR, the best standard of care for treatment of out-of-hospital cardiac arrest in the United States today. There was a 52% increase in survival to hospital discharge with favorable neurologic function (primary study endpoint) in subjects with an OHCA of presumed cardiac etiology (mITT population) treated with the ResQCPR System (75/838) compared with conventional CPR (47/800) (p=0.019). One year after OHCA, greater than 95% of surviving subjects in both treatment groups had excellent neurological function, as determined by cognitive, functional, and quality of life testing. Subjects treated with the ResQCPR System and S-CPR had similar adverse event rates. The only difference in adverse events was an increase in pulmonary edema in the ResQCPR group which did not affect survival to hospital discharge with good neurological function. Given the high prevalence and devastating nature of cardiac arrest, lack of alternative effective therapies, and better efficacy of the ResQCPR System versus the best available standard-of-care CPR technique, it is concluded that the benefits of the ResQCPR device system for the treatment of patients with cardiac arrest outweigh the risks. This conclusion is supported even further by the device system's excellent safety profile and increased one year survival with restoration of normal or nearly normal neurologic function.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Four European clinical studies have evaluated the hemodynamic effects, safety and clinical effectiveness of the ResQPOD ITD 16 and the ResQPUMP, as summarized in **Table 11**. These clinical studies demonstrated that use of ResQCPR prototypes resulted in improved hemodynamics, lower intrathoracic pressures during the chest decompression phase, increased circulation as measured by end tidal CO_2, and increased 1- and 24-hour survival rates. The physiologic and clinical outcomes in these studies are consistent with the findings in the pivotal ResQTrial. There were no safety concerns raised by these four

clinical studies that included a total of 644 patients. Taken together, these four European studies provide evidence of a favorable risk/benefit profile, and support for the overall safety and efficacy of use of the ResQCPR System for treatment of patients with cardiac arrest.

Table 11: Published Peer-Reviewed Clinical Studies of ResQPOD ITD 16 and the CardioPump (ResQPUMP)*

Journal Citation (reference)	CPR Method	Design	Control Group (n)	Group w/ Active ITD (n)	Endpoints	Results	P Value; Odds Ratio (95% CI)**
Plaisance et al. *Circulation*, 2000[9]	CardioPump ± ResQPOD ITD 16 (sham vs. active ITD)	Prospective, single center, blinded, randomized; pre-hospital	10	11	systolic arterial pressure (mean peak) diastolic arterial pressure (mean peak)	Sham: 90 ± 6.4 mmHg Active: 108 ± 3.1 mmHg Sham: 36.5 ± 1.5 mmHg Active: 56.4 ± 1.7 mmHg	p < 0.05 p < 0.001

Wolcke et al. *Circulation*, 2003[12]	S-CPR vs. ResQCPR	Prospective, single-center randomized; pre-hospital	107	103	1°: Survival to 1 hour after witnessed arrest – all pts
					
					2°: Survival to 1 hour after witnessed arrest – V-fib pts
						s-CPR: 32%
						ACD-ITD: 51%
						
						s-CPR (n=38): 27%
						ACD-ITD (n=46): 68%
							p = 0.006;
							2.4 (1.28, 4.62)
							
							p = 0.02;
							5.7 (2.07, 15.9)

Plaisance et al. *Resuscitation*, 2004[10]	CardioPump ± ResQPOD ITD 16 (sham vs. active)	Prospective, multicenter, blinded, randomized; pre-hospital	200	200	Survival to 24 hours – all pts	Sham: 22% Active: 32%	p = 0.02; 1.67 (1.07, 2.60)
Plaisance et al. *Crit Care Med* 2005[11]	CardioPump ± ResQPOD ITD 16 (sham vs. active)	Prospective, Single-center, blinded, randomized; pre-hospital	13	13	1°: Mean peak negative intrathoracic pressure during decompression with facemask 1°: Mean peak negative intrathoracic pressure during decompression with ET tube 2°: Mean peak negative intrathoracic pressure during decompression	Sham: -1.0 ± 0.73 mmHg Active: -4.6 ± 3.7 mmHg Sham: -1.3 ± 1.3 mmHg Active: -7.3 ± 4.5 mmHg Active ITD w/ facemask (n=13): -4.6 ± 3.7 mmHg Active ITD w/ ET (n=13): -7.3 ± 4.5 mmHg	p = 0.003 p = 0.001 p = NS

*For all studies shown, the significant p- values shown favor the ACD-CPR/active ITD study group. See reference section for complete references.
** Odds ratio (OR) and 95% confidence interval (CI), as applicable

XI. CONCLUSIONS DRAWN FROM THE NON-CLINICAL AND CLINICAL STUDIES

Risk/Benefit Conclusions

The ResQCPR System is externally applied during CPR to help improve circulation to the heart and brain and increase neurologically intact survival from sudden cardiac arrest. Increasing survival from sudden cardiac arrest introduces the potential risk that more survivors may not have good neurologic function. However, the clinical results from the ResQTrial demonstrated that the overall number of survivors increased with the ResQCPR System without an increase in the percentage of survivors with poor neurologic function.

Inherent in the use of any technology is the potential risk of device malfunction, incorrect use or a delay in treatment while the device is being deployed. The analysis of these risks for the ResQCPR System must consider that standard CPR is always available for the caregiver to provide. In the event of a delay in use of the ResQCPR System at the scene of a sudden cardiac arrest, device malfunction or incorrect use, the responder can always revert to standard CPR. The patient may not receive the full benefit of the ResQCPR in these circumstances, but there is no risk that the patient will receive a less effective treatment than he or she receives today as standard of care.

From a device design perspective, the ResQPump introduces the potential risk of using too much downward or upward force during chest compressions and decompressions, which could result in an increase in chest fractures and organ damage. This potential risk may also occur with S-CPR. The ResQPUMP has both a visual force gauge that gives feedback on applied compression and decompression forces and a metronome to give feedback on the proper rate of compression and decompressions. The design of the ResQPOD introduces the risk of occluding the airway should a subject regain a pulse and spontaneous respiratory effort. This risk is mitigated by a safety check valve inside the device that allows for spontaneous inspiration.

The safety data provided by the ResQTrial demonstrated consistency across the patient population and raised no unique concerns with the ResQCPR System. The only difference in adverse events was an increase in pulmonary edema in the ResQCPR group which did not affect survival to hospital discharge with good neurological function.

Finally, the risk profile of the ResQCPR System will be reduced further through a robust training program for all users of the device. This training program has been developed based upon the experience gained from training nearly 5000 medics during the ResQTrial.

The ResQCPR System has a well-established mechanism of action for improving blood flow to the brain and other vital organs during sudden cardiac arrest. It is designed to improve CPR physiology by lowering intrathoracic pressure, enhancing venous return to the heart, and increasing cardiac output and blood flow to vital organs during CPR. When S-CPR is performed correctly, it typically provides only 10 – 20% of normal blood flow to the heart, and 20 – 30% of normal blood flow to the brain.[13] Without adequate circulation, the chances of resuscitating a patient in cardiac arrest are significantly reduced. The ResQCPR System was designed to provide 2-3 times more circulation to the heart and brain (normal blood flow to the brain and 70% of normal blood flow to the heart) than is possible with S-CPR alone, as demonstrated in an animal model.[14]

In addition to the physiologic benefit, the ResQCPR System also incorporates feedback mechanisms to help guide high-quality CPR. This includes a force gauge to provide feedback on compression/decompression force and metronomes to guide the timing of compressions and ventilations. This is important since the effectiveness of CPR can vary significantly based on compression rate, compression depth and timing of ventilation.

A total of 1,655 subjects enrolled in the pivotal ResQTrial met criteria for the primary mITT analysis population and were evenly distributed between the S-CPR and ResQCPR System study arms. Differences in the rates of survival to hospital discharge with favorable neurological function were significantly higher in the ResQCPR study arm: there was a relative 52% increase in survival with favorable neurological outcomes (5.9% [47/800] vs. 8.9% [75/838]) (p=0.019). In addition, there were 49 % more survivors 90 days and one year after cardiac arrest in the ResQCPR treatment group (74/840 with ACD+ITD versus 48/813 with S-CPR, p=0.03). Among those who survived in both groups, there was no evidence of diminished neurological function. There was also a benefit in the entire ITT population. For all 2470 non-traumatic OHCA subjects in the ITT population randomized in the pivotal phase of the study, 6.0% survived to hospital discharge with favorable neurological function after treatment with S-CPR versus 8.0% in the ResQCPR System group (p=0.057). This included subjects with non-cardiac etiologies. The benefit of the ResQCPR System devices in terms of survival with satisfactory neurological function was observed at all time points in the study, across study sites, and regardless of age and gender.

The ResQTrial demonstrated that the ResQCPR System can be efficiently deployed in the pre-hospital basic life support setting. The average time to device deployment upon arrival at the scene by the caregiver for all subjects without an EMS witnessed arrest and randomized to ResQCPR was less than 45 seconds. This is important since early intervention during sudden cardiac arrest provides the greatest opportunity for survival.

If the device were approved and were adopted widely, based on the results of the ResQTrial, the ResQCPR System would present an opportunity to save thousands more lives in the United States per year in the pre-hospital sudden cardiac arrest population.

Overall Conclusions
Cardiac arrest is a devastating event requiring immediate intervention if there is to be any possibility for survival. Approximately 1000 people die from OHCA each day in the U.S., making this epidemic the nation's number one killer. Despite 50 years of effort, survival rates from cardiac arrest remain dismal. There are no alternative therapies to the ResQCPR System that have been approved for use by the FDA to increase neurologically intact survival from cardiac arrest. The benefits of the ResQCPR System, which has been demonstrated to provide a significant increase in neurologically intact survival to hospital discharge and increased long-term survival up to one year, clearly outweigh the relatively low risks associated with this device.

XII. PANEL RECOMMENDATION [To be completed by FDA]

The clinical data provided by the company to support the indications for use being requested was reviewed by the Circulatory System Devices Advisory Panel on May 6, 2014. The panel recommended approval of the ResQCPR System for use in the treatment of [disease condition].

XII. CDRH DECISION [To be completed by FDA]

CDRH concurred with the Circulatory System Devices Advisory Panel recommendation of _____ and issued an approval order on _____. The device manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 C.F.R. Part 820).

XII. APPROVAL SPECIFICATIONS

[To be completed by FDA]

XII. REFERENCES

1. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122:S720-S728.

2. Lurie KG, Coffeen P, Shultz J, McKnite S, Detloff B, Mulligan K. Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. *Circulation.* Mar 15 1995;91(6):1629-1632.

3. Voelckel WG, Lurie KG, Sweeney M, et al. Effects of active compression-decompression cardiopulmonary resuscitation with the inspiratory threshold valve in a young porcine model of cardiac arrest. *Pediatric research.* Apr 2002;51(4):523-527.

4. Lurie K, Voelckel W, Plaisance P, et al. Use of an inspiratory impedance threshold valve during cardiopulmonary resuscitation: a progress report. *Resuscitation.* May 2000;44(3):219-230.

5. Bahlmann L, Klaus S, Baumeier W, et al. Brain metabolism during cardiopulmonary resuscitation assessed with microdialysis. *Resuscitation.* Nov 2003;59(2):255-260.

6. Metzger A, Herman M, McKnite S, D Y, Lurie K. Effect of an impedance threshold device and a novel active compression decompression cardiopulmonary resuscitation device on cerebral perfusion pressures and 24-hour neurological survival in a porcine model of cardiac arrest. *Circulation.* 2006;114(18):II-554.

7. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. *Lancet.* Jan 22 2011;377(9762):301-311.

8. Cummins R, Chamberlain D, Abramson N. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrst: the Utstein Style. *Circulation.* 1991;84(2):960-975.

9. Plaisance P, Lurie K, Payen D. Inspiratory impedance during ACD CPR: a randomized evaluation in patients in cardiac arrest. *Circulation.* 2000;101(9):989-994.

10. Plaisance P, Lurie KG, Vicaut E, et al. Evaluation of an impedance threshold device in patients receiving active compression-decompression cardiopulmonary resuscitation for out of hospital cardiac arrest. *Resuscitation.* Jun 2004;61(3):265-271.

11. Plaisance P, Soleil C, Lurie KG, Vicaut E, Ducros L, Payen D. Use of an inspiratory impedance threshold device on a facemask and endotracheal tube to reduce intrathoracic pressures during the decompression phase of active compression-decompression cardiopulmonary resuscitation. *Critical care medicine.* May 2005;33(5):990-994.

12. Wolcke BB, Mauer DK, Schoefmann MF, et al. Comparison of standard cardiopulmonary resuscitation versus the combination of active compression-decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. *Circulation.* Nov 4 2003;108(18):2201-2205.

13. Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest: A policy statement from the American Heart Association. *Circulation.* Feb 9 2010;121(5):709-729.

14. Lurie KG, Mulligan KA, McKnite S, Detloff B, Lindstrom P, Lindner KH. Optimizing standard cardiopulmonary resuscitation with an inspiratory impedance threshold valve. *Chest.* Apr 1998;113(4):1084-1090.